The measure of the land and the measure of our bodies are the same . . .

I never said the land was mine to do with as I chose. The one who has
the right to dispose of it is the one who created it.

Chief Joseph, Nez Perce

EPA Releases Mercury Report

December 19 was a big day for the U.S. EPA. On that day, after several years of debate and angst, the EPA released the draft copy of its *Report to Congress on Mercury*, an eight-volume review of the hazards of mercury, including an inventory of exposures and health effects caused by mercury emissions. The EPA calls its report a "snapshot" of the current state of mercury emissions—and of the current body of knowledge on the topic, which only very recently expanded to include information from studies conducted in the Seychelle Islands and the Faroe Islands.

There is no longer any doubt that exposure to mercury, particularly to the organic form methylmercury, causes damaging health effects, but there is fierce debate over what level of exposure should be considered dangerous. The EPA report, which was originally due in 1994, was repeatedly held up in hopes of including data from more recent studies, such as the Seychelles study. The agency finally decided to release the report without those data; the report relies instead largely upon a study from the early 1970s of Iraqi mother-child pairs, which found that the presence of mercury in the mother's hair at levels over 10 parts per million appears to be related to developmental and/or neurological abnormalities in her offspring. Based upon those findings, the EPA proposes a reference dose for methylmercury of 0.1 µg per kilogram body weight per day—a figure that is five times more stringent than that proposed by the Agency for Toxic Substances and Disease Registry (ATSDR) and over four times as tough as that of the Food and Drug Administration.

The Seychelle Islands study was designed as a follow-up to the Iraqi study. Its purpose was to test the Iraqi findings on a population that was both much larger than the Iraqi population and that received its mercury exposure through the most common route of consumption of fish (the Iraqi subjects had eaten contaminated grain). The findings of the Seychelles study, published in volumes 16 and 18 (1995 and 1997, respectively) of Neurotoxicology, found no evidence that prenatal methylmercury exposure is linked to childhood defects. However, a companion study of subjects from the Faroe Islands, published in the November-December 1997 issue of Neurotoxicology and Teratology, indicates that methylmercury exposure in utero does cause negative health effects—but not at the rates noted in the Iraqi study.

The ATSDR has just issued its own draft report on the health effects of mercury. Christopher T. DeRosa, director of the division of toxicology at the ATSDR, says of the EPA report, "We feel it's a significant body of work. . . . Its conclusions are consistent with conclusions reached by the ATSDR in our 1993 report." DeRosa says that the newest ATSDR report includes data from the Seychelle Islands study. The final form of the report will include the data from the Faroe Islands study, which were not available at the time the draft was drawn up.

Opponents of the EPA report say the agency is being overreactive in its play to have mercury labeled as a significant health threat. Many of these opponents feel the EPA report will alarm U.S. citizens unnecessarily by leading them to believe that less, rather than more,

mercury will cause health problems, particularly to those exposed *in utero*.

Humans are exposed to methylmercury primarily through eating fish that have accumulated amounts of the compound in their muscle tissue. In general, U.S. fish fanciers are less likely to eat contaminated fish than consumers in other nations. Still, there is some danger to those who eat large amounts of seafood, particularly large predatory species such as shark and swordfish, which are more likely, through their position in the food chain, to have been exposed to mercury pollution.

The birth of the industrial age gave rise to increased releases of mercury, thanks to such developments as electricity, nuclear energy, and fossil fuel combustion. Mercury tends to spread widely and easily because it can remain suspended in the atmosphere for up to a year. The organic forms of mercury such as methylmercury are the more dangerous to humans because these forms tend to bioaccumulate, as opposed to the inorganic forms, which tend to be less well absorbed and more easily discarded by the body.

The uncertainty over whether it is safe to eat fish and in what amounts is frightening to many people. To alleviate these fears, DeRosa says, representatives from a number of government agencies, including the EPA, the ATSDR, and the FDA, will issue a joint statement later this year that will attempt to provide a consensus of where the science of mercury poisoning is heading.

Fighting Disease with Disease

For nearly 200 years, people have observed that cancers occasionally regress in patients who contract a bacterial infection. However, purposely infecting cancer patients with the same bugs that cause food poisoning and toxic shock syndrome in order to control their tumors has never seemed like a very sensible treatment regimen—until, perhaps, now. In October, researchers at the Yale University School of Medicine in New Haven, Connecticut, announced they had developed a strain of Salmonella typhimurium with an unusual affinity for malignant tumors. Not only does this strain limit cancer growth while posing a minimal risk of serious infection, it also can be used to deliver anticancer agents to the site of the tumor.

The result is a *Salmonella* that attacks tumors via a two-pronged method, but that does little or no harm to the patient. In the Yale study, cancerous mice that received the bacteria treatment lived up to twice as long as

Comparison of Two Primary Studies on Exposure to Methylmercury

	Iraqi study ^a	Seychelles study ^b
Study type	Retrospective study	Prospective longitudinal study
Number of participants	Approximately 80 mothers with infants	Over 700 mothers with infants
Medium of exposure	Ingestion of tainted grain	Ingestion of tainted fish
Exposure duration	One exposure episode lasting several months; few low-level exposures	Low-level, long-term exposures, including exposures during pregnancy and lactation
Method of collecting exposure data	Used samples of scalp and non-scalp hair	Used only scalp hair
Method of collecting health effects data	Self-reporting by participants	Collected by health professionals using neurobehavioral tests
Methylmercury levels found in maternal hair	10 to several hundred parts per million	0.5–26.7 parts per million

^aNeurotoxicol 16(4):583-716 (1995) and 18(3):819-829 (1997).

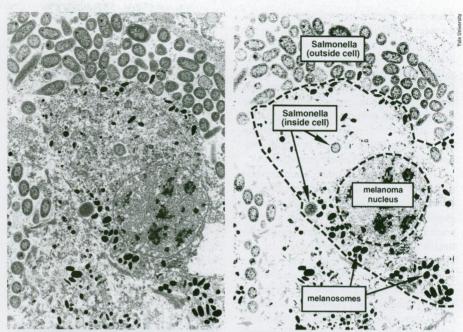
^bNeurotoxicol Teratol 19(6):417–428 (1997)

cancerous mice that did not, and were found to have tumors less than half the size of those in the untreated mice. The researchers showed the method to be effective against a wide range of tumors, including those caused by inoculating mice with human lung, colon, breast, kidney, and liver cancers. The Salmonella even effectively battled multiple tumors within the same animal, the researchers reported in the 15 October 1997 issue of Cancer Research.

The mechanism by which bacterial infections slow cancer growth is not known, but investigator John Pawelek and colleagues Brooks Low and David Bermudes at Yale reasoned that if such an infection was localized to the tumor site, it would slow the cancer growth more effectively while reducing the risk of infection elsewhere in the body. By using different growth substrates, the team was able to isolate a mutant form of Salmonella that needs an unusual mix of metabolites to grow—a mix found in abundance within malignant tumors but scarcely anywhere else in the body. Once injected into a cancerous mouse, the mutant Salmonella seeks out the tumor and thrives there, while the immune system easily controls the bug in the rest of the body. Sacrificed mice that had undergone treatment had Salmonella populations in their tumors that were 250-9,000 times as dense as those found in the animals' livers.

The deliberate infections dramatically reduced tumor growth, but the authors decided to take the research a step further. They reasoned that, because their Salmonella strain tended to concentrate itself around tumors, it would make a good vehicle for delivering anticancer drugs. In this vein, the researchers further modified the strain by introducing into the bacteria the herpes simplex virus gene that codes for thymidine kinase. While thymidine kinase does not fight cancer on its own, it is deadly to cells when combined with ganciclovir, a prodrug used to fight herpes in AIDS patients. By a very poorly understood process, cells that produce thymidine kinase, such as the Yale team's modified Salmonella, will not only die upon contact with ganciclovir, they will take their nearest neighbors with them. This so-called "bystander effect," which was first noted a decade ago, has been observed in many instances of cell death.

The researchers injected mice with the Salmonella that incorporated the thymidine kinase gene, and then treated them with ganciclovir. As expected, additional tumor regression due to the bystander effect was noted. However, the researchers reported, this effect was small in comparison to the much more radical effect of the bacterial infection on the tumor, despite the efficacy of the drug. Nonetheless, the use of Salmonella as a drug delivery device still represents an important



Salmonella soldiers? Mice injected with *Salmonella* show that the bacteria make their way into melanoma tumor cells and multiply, slowing the growth of the tumor.

breakthrough. Getting drugs into tumors has always been a difficult challenge for doctors because, among other barriers, tumors have high internal pressure pushing outward. But the Yale scientists showed that for motile *Salmonella* such obstacles are no problem.

The October report by the Yale group was the culmination of four years of research on this radical new method to fight cancer. Now the scientists are preparing the invention for use in clinical trials, the next step in drug development.

Is Airborne Manganese a Hazard?

Public health officials, scientists, and regulators worry that a gasoline additive containing manganese, claimed by its maker to boost engine performance, may cause physical harm by increasing the amount of manganese in the air. Ethyl Corporation of Richmond, Virginia, which makes methylcyclopentadienyl manganese tricarbonyl (MMT), disputes such worries, and says the manganese emitted into the air when MMT is burned poses no risk to human health.

The concerns about the additive come as the Agency for Toxic Substances and Disease Registry (ASTDR) is completing a toxicological profile of manganese to assess sources of exposure and the metal's impact on health. The agency is required to prepare such profiles for hazardous substances found at the nation's most serious hazardous waste sites—those on the EPA's National Priorities List of Superfund sites. Of 1,430 sites on the list, 644 (or 45%) have "excessive levels of manganese," according to the ATSDR. Excessive

levels are those greater than background in the environment.

A trace element, manganese is an essential part of the diet and can easily be obtained from grains and nuts. Manganese deficiency can lead to bone problems and stunted growth. Excess dietary manganese is simply excreted. A number of studies have shown that occupational exposure to manganese can lead to Parkinson's disease-like symptoms such as muscle tremors.

Manganese is used to give strength to steel and aluminum. Manganese levels in the air can vary widely, being higher near foundries and metal plants and lower away from such facilities. But it's chronic exposure to manganese compounds emitted in the exhaust of vehicles fueled by MMT-boosted gas that has raised the most concerns.

Canada banned the import of MMT this year—none of the additive is made there—due to concerns over possible health effects. MMT had been used in Canadian gasoline for nearly 20 years. Ethyl is fighting the ban. A U.S. appeals court in Washington, DC, overturned an EPA ban on MMT in 1995, saying the agency acted illegally by attempting to ban the additive on health grounds under the Clean Air Act (CAA). The court said that under the CAA, the EPA could only consider MMT's effect on engine performance. But California has successfully kept the additive out of unleaded gasoline sold in that state for approximately 20 years because of a "lack of data on the health effects of breathing manganese," says Richard Vincent, a spokesman for the California Air Resources Board.

Widespread exposure to manganese, says Michael Davis, senior health scientist and acting chief of the EPA's Hazardous Pollutant